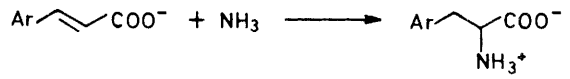
# Addition of Amine Nitrogen to an Unactivated Double Bond. The Mechanisms of the Reverse Hofmann Elimination

By **Anthony J. Kirby** * and **Christopher J. Logan**, University Chemical Laboratory, Cambridge CB2 1EW

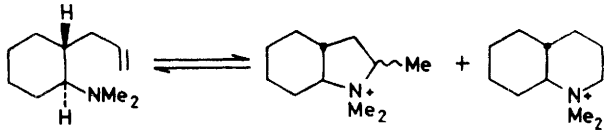
The tertiary amino-group of amine (7) adds to the transannular double bond with a half-life of 3.3 s at 25°. Reaction is general acid catalysed, and a mechanism is proposed in which nucleophilic addition of amine nitrogen to one end of the double bond is concerted with the transfer of a proton from the general acid to the other. The reaction is observed only with systems in which substantial ground state strain is relieved on cyclisation. It gives the products of antiperiplanar addition, and represents the microscopic reverse of the Hofmann elimination. The reverse Hofmann reaction as normally carried out under acidic conditions is a much slower reaction, much less sensitive to structure, which goes by a quite different mechanism. The cyclisation of amine (8), for example, is specific acid catalysed and probably involves a carbonium ion intermediate.

THIS work stems from an interest in the mechanism of action of the amino-acid ammonia lyases.[1] The reactions catalysed by the histidine [2] and phenylalanine [3] enzymes have been shown to be reversible: thus these enzymes can catalyse the overall addition of ammonia to an unactivated double bond. This is a reaction with-



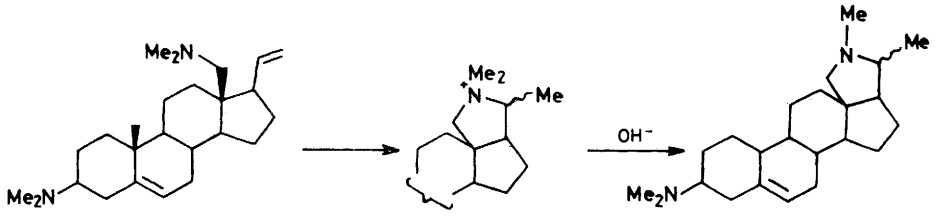
out close chemical precedent, apart from the slow addition of ammonia to fumarate dianion studied by Bada and Miller.[4] These authors calculated a half-life of nearly two weeks for this reaction, at 100° in aqueous 1M-$NH_3$, from the rate and equilibrium constants for the deamination of aspartate. However, even the dianion of fumaric acid cannot be considered entirely unactivated towards nucleophilic addition, since the carboxylate group can stabilise an adjacent carbanion significantly.[5] Nevertheless, this result gives sufficient grounds to expect that the corresponding intramolecular addition of amine nitrogen to an entirely unactivated double bond might occur under mild conditions in a suitable system activated by ground state strain, where effective molarities of intramolecular nucleophile of the order of $10^{10}$M should be attainable.[6]

In fact intramolecular addition of amine nitrogen to unactivated double bonds is a known reaction. Suitable aminoalkenes are generated by the Hoffmann elimination from cyclic quaternary ammonium salts, so that known examples involve almost exclusively the addition of tertiary nitrogen. Thus Haworth and McKenna and their co-workers have shown that aminoalkenes such as (1) are cyclised on boiling for a few hours in acetic acid to the quaternary acetates (2) (major product) and (3).[7a] An extensive series of investigations [7] showed that many 4- and 5-dimethylaminoalkenes are cyclised under these conditions: and that in one or two particularly favour-



(1) (2) (3)

able systems the reaction also occurs in neutral or basic hydroxylic solvents. For example, the aminoalkene (4), derived from conessine, gives the alkaloid heteroconessine (5) on heating for 6 h at 150° in aqueous alkaline ethylene glycol.[8]

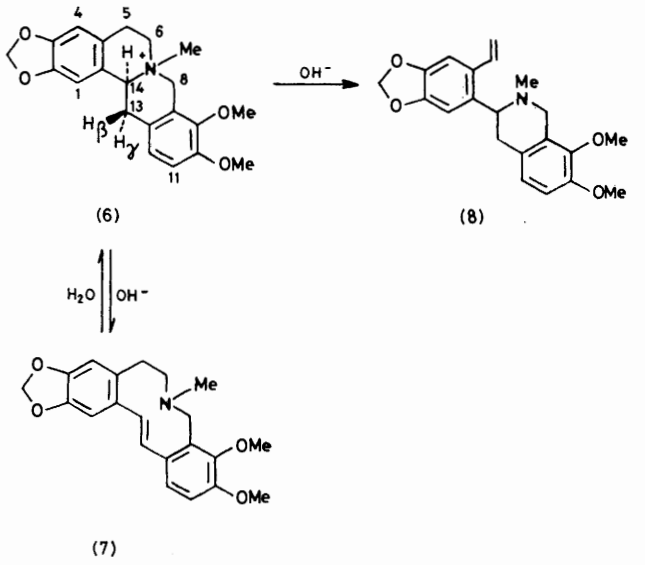


(4) (5)

We have chosen to study the similar reactions of the Hofmann degradation products of *N*-methyltetrahydroberberinium hydroxide (6). The reactions shown in Scheme 1 were first identified by Pyman.[9] The base (7) is the major product when the quaternary ammonium

[1] K. R. Hanson and E. A. Havir, 'The Enzymes,' ed. P. D. Boyer, Academic Press, New York, 1972, 3rd edn., vol. 7, p. 75.
[2] V. R. Williams and J. M. Hiroms, *Biochem. Biophys. Acta*, 1967, **139**, 214; C. B. Klee, K. L. Kirk, L. A. Cohen, and P. McPhie, *J. Biol. Chem.*, 1975, **250**, 5033.
[3] K. R. Hanson and E. A. Havir, *Biochemistry*, 1968, **7**, 1904.
[4] J. L. Bada and S. L. Miller, *J. Amer. Chem. Soc.*, 1970, **92**, 2744.
[5] A. J. Kirby and G. J. Lloyd, *J.C.S. Perkin II*, 1976, 1762.
[6] A. J. Kirby and G. J. Lloyd, *J.C.S. Perkin II*, 1976, 1753.
[7] (*a*) B. Bailey, R. D. Haworth, and J. McKenna, *J. Chem. Soc.*, 1954, 967; (*b*) R. D. Haworth, J. McKenna, R. G. Powell, and P. Woodward, *ibid.*, 1951, 1736; (*c*) J. McKenna and A. Tulley, *ibid.*, 1960, 945; (*d*) K. Jewers and J. McKenna, *ibid.*, p. 1575; (*e*) E. N. Wall and J. McKenna, *J. Chem. Soc.* (*C*), 1970, 188.
[8] H. Favre, R. D. Haworth, J. McKenna, R. G. Powell, and G. H. Whitfield, *J. Chem. Soc.*, 1953, 115.
[9] F. L. Pyman and H. A. D. Jowett, *J. Chem. Soc.*, 1913, **103**, 290; F. L. Pyman, *ibid.*, p. 817.

hydroxide is evaporated to dryness under reduced pressure, but the thermodynamic product (8) is produced when the reaction is carried out at atmospheric pressure.




(6) (8) (7)

SCHEME 1

When a solution of (7) in aqueous ethanol is heated the quaternary ammonium hydroxide is reformed.[9] More recently Russell [10] showed that the cyclisation reaction proceeds more slowly in acetic acid or dilute HCl.

## EXPERIMENTAL

*Materials.*—Inorganic salts were of analytical grade. AnalaR dioxan was purified by refluxing over sodium metal (3 gm per 100 ml) for 24 h or until the metal remained bright, whichever was the longer, followed by fractional distillation. The fraction boiling over the range 101 ± 0.5° was collected and stored in the dark over 4 Å molecular sieves. Distilled water was distilled twice more from all glass apparatus.

*trans*-9,10-Dimethoxy-7-methyl-2,3-methylenedioxy-5,6,7,8-tetrahydro[*c*,*g*]azecin (7) (Pyman's base A) was prepared according to Pyman's directions.[9] The modifications reported by Russell [10] were found to produce complications and to reduce the overall yield. Several recrystallisations from ethyl acetate (freshly distilled from $P_2O_5$) had to be carried out under nitrogen before colourless microcrystalline (7) was obtained, m.p. 134—136° (lit.,[9] 135—136°), $M^+$ 353.163 0 (within 0.003 0 of calculated value); $\lambda_{max.}$ (95% EtOH) 295 nm (ε 4 370); δ (100 MHz, $CDCl_3$) 7.09 (1 H, d, *J* 16 Hz, *trans*-olefin), 6.99 (2 H, s, H-11, -12); 6.82 (1 H, s, H-1), 6.62 (1 H, s, H-4), 6.43 (1 H, d, *J* 16 Hz, *trans*-olefin), 5.89 (2 H, s, methylenedioxy), 3.84 (3 H, s, OMe), 3.78 (3 H, s, OMe), 2.72 (4 H, s, H-5, -6), and 2.21 (3 H, s, NMe). 7,8-Dimethoxy-2-methyl-3-(4,5-methylenedioxy-2-vinylphenyl)-1,2,3,4-tetrahydroisoquinoline [9] (8) (Pyman's base B) had m.p. 115—116.5° (lit.,[9] 114—115°); $\lambda_{max.}$ (95% EtOH) 300 (ε 4 870) and 262 nm (1 780); $M^+$ 353; δ($CDCl_3$) 7.17 (1 H, dd, *J* 17, 11 Hz, H-6), 5.46 (1 H, d, *J* 17 Hz, *trans* olefin, H-7), and 5.16 (1 H, d, *J* 11 Hz, *cis* olefin, H-7′). The coupling of the geminal protons is not fully resolved.

*Cyclisation Product of* (8).—Compound (8) was heated at 50° for 3 days in 1M-HCl in 20% dioxan–water. The solution was evaporated to dryness to give a solid (15), m.p. 204—207°, $M^+$ 354; δ($CD_3OD$–$C_6D_6$, 100 MHz) 6.97 (2 H, s), 6.90 (2 H, s), 6.02 (2 H, s, methylenedioxy), 5.64—3.00 (6 H, m, alicyclic), 3.93 (3 H, s, OMe), 3.88 (3 H, s, OMe), 2.68 (3 H, s, NMe), and 1.32 (3 H, m, CMe). This compound differed from *N*-methyltetrahydroberberinium chloride in m.p., n.m.r., mass spectral fragmentation pattern, and solubility. N.m.r. suggests that it is (the expected) isoindoline (15), formed as a mixture of similar amounts of the two epimers at the point of ring closure. The 3-proton multiplet at δ 1.32 is made up of three peaks of relative height 1 : 1 : 2, interpreted as a pair of superimposed C–Me doublets, $J_{vic}$ 5 and 11 Hz.

*Stereospecificity of Cyclisation of Base* (7).—The cyclisation of (7) under mildly basic conditions gives the *N*-methyltetrahydroberinium cation (6) in quantitative yield, by the addition to the stilbene double bond of the transannular nitrogen atom, and a proton. A small sample of (7), dissolved in dry dioxan (10 mg per 10 ml), was injected into an equal volume of 0.01N-NaOD in $D_2O$ and left at room temperature until monitoring of small portions by u.v. showed that cyclisation was complete. The pH of the solution was adjusted to <2 by the addition of 1N-HCl, and the *N*-methyltetrahydroberberinium chloride obtained by evaporating the solution to dryness. The high resolution mass spectrum showed that only monodeuterio-*N*-methyltetrahydroberberine was present, and that no di- or tri-deuterio-species were formed.

The stereochemistry of deuteriation was assigned by n.m.r. (assignments were helped by the publication of the 300 MHz spectrum of tetrahydroberberine by Jeffs and Scharver [11] while this part of the work was in progress). The monodeuterio-compound was taken up in [$^2H_6$]DMSO and filtered to remove NaCl. The 220 MHz spectrum (run by P.C.M.U., Harwell) of the protio-compound (6) shows a broad multiplet, δ 3.8 (2 H), for the protons at C-13, which changes shape and integrates for a single proton in the deuteriated product. The proton at C-14 appears as a well resolved double doublet in the spectrum of the protio-compound (6) δ 4.77 (*J* 4 and 15 Hz). The larger coupling constant is assigned to the (*trans*) coupling with 13-$H_\beta$, and the smaller to the *cis*-coupling with 13-$H_\alpha$. In the spectrum of the monodeuterio-compound the proton at C-14 appears as a simple doublet (*J* 15 Hz). Evidently 13-$H_\beta$ is still present, and the deuteron is in the α-position at C-13 as expected for antiperiplanar addition; and as found also for the formation of monodeuteriotetrahydroberberine by Jeffs and Scharver.[11]

Two other n.m.r. experiments confirm this assignment. Space-filling models show a very close through-space interaction between 13-$H_\alpha$ and the C-1 aromatic hydrogen (the hydrogen atoms are in contact in the model). The major mechanism for relaxation of nuclei of spin ½ in deuteriated solvents at high dilution is through intramolecular dipole–dipole interactions, which show an $r^{-6}$ dependence on the distance between nuclei.[12] The major source of relaxation of the well resolved aromatic proton might therefore be expected to be 13-$H_\alpha$. Relaxation times were measured for all the aromatic protons (Varian XL 100 instrument) of (6), and of its [13-$^2H_\alpha$] derivative. The values obtained

[10] P. B. Russell, *J. Amer. Chem. Soc.*, 1956, **78**, 3115.
[11] P. W. Jeffs and J. D. Scharver, *J. Amer. Chem. Soc.*, 1976, **98**, 4301.
[12] J. H. Noggle and R. E. Schirmer, ' The Nuclear Overhauser Effect. Chemical Applications,' Academic Press, New York, 1971, pp. 21, 25.

(deuterio-compound in parentheses), C-1, 0.41 (0.79); C-4, 0.81 (0.89), C-11, -12, 0.33 (0.41) s, show that the relaxation time for the aromatic proton close to the deuteron at C-13 has almost doubled.

A nuclear Overhauser effect experiment gave similar results. Irradiation of the C-13 proton peak caused similar small decreases (2—5%) in the integrated intensity of each of the aromatic proton signals of the [13-$^2H_\alpha$] compound, but a large *increase* (24%) in the integrated intensity of the C-1 proton of the protio-compound, as expected if the relaxations of this and the 13α-proton are closely coupled, as a result of their close proximity.

## RESULTS

The rates of cyclisation of the bases (7) and (8) were measured in 20% dioxan–water, with pH controlled by

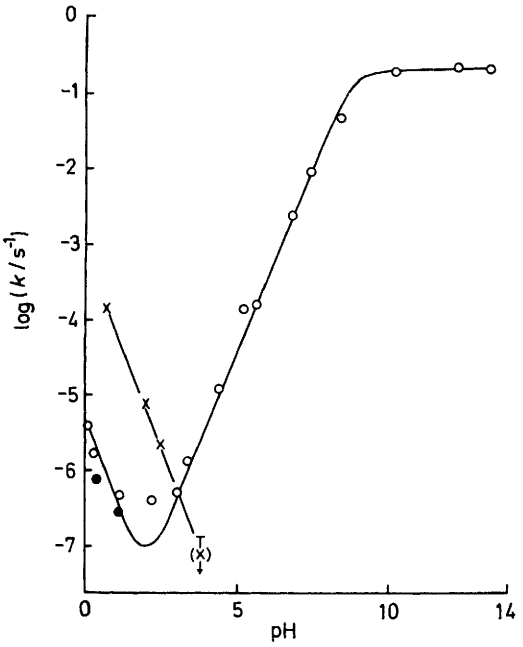



FIGURE 1 pH–Rate profiles for (i) the cyclisation of amine (7) (○) at 25° (the points are experimental, the curve calculated from the derived constants, given in Table 1) and (ii) the cyclisation of amine (8) at 50° (×). Two measurements for this latter reaction at 25° (●) show that (7) and (8) react at very similar rates under acidic conditions

HCl, NaOH, and the buffers listed in Table 2, and ionic strength brought to 1M (KCl). Reactions were initiated by injecting *ca.* 40 μl of a stock solution of the base in dioxan (*ca.* 1 mg ml$^{-1}$) into buffer (2 ml) preincubated in the cuvette at the temperature of the experiment [usually 25.0 ± 0.1°, but 50.0 ± 0.1° for the slow reactions of (8)]. The buffer was always present in at least 100 fold excess, and only first-order kinetics were observed. Reactions were followed at 310 (7) or 270 nm (8), in the thermostatted cell compartment of a Zeiss PMQ II spectrophotometer; and the pH measured at the end of each run, using an EIL Vibron Electrometer 33B fitted with a C33B pH-measuring unit (pH 3—10), or a Radiometer pHM 64 pH meter, with a Pye–Ingold semi-micro combination electrode 401 M5 E07. Meter and electrode were calibrated according to British Standard 1647 (1961).

pH–Rate profiles for the cyclisation reactions are shown in Figure 1. The reaction of amine (8) is too slow to measure above pH *ca.* 3, and only an acid catalysed reaction is apparent. The rate in chloroacetate buffers (pH 2.4) did not depend significantly on buffer concentration, and log $k_{obs}$ depends on pH with a slope close to −1, so the reaction appears to be specific acid catalysed.

TABLE 1

Data for the cyclisation of amine (7) at 25° and ionic strength 1.0M in 20% dioxan–water

| | |
|---|---|
| $pK_a$ [a] | 8.77 ± 0.001 |
| $k_o$ [a] | 2.09 ± 0.08 × 10$^{-1}$ s$^{-1}$ |
| $k_o(D_2O)$ [b] | 1.23 ± 0.03 × 10$^{-1}$ s$^{-1}$ |
| $k_H/k_D$ | 1.70 ± 0.04 |
| $\Delta H^{\ddagger}$ [c] | 12.99 ± 0.01 kcal mol$^{-1}$ |
| $\Delta S^{\ddagger}_{298}$ | −18.0 ± 0.4 cal mol$^{-1}$ K$^{-1}$ |

[a] From least squares analysis of pH rate profile above pH 3 (14 data sets). [b] Five data sets. [c] See text.

Amine (7) shows a similar acid catalysed reaction at low pH [less than twice as fast as that of (8)] but is cyclised very rapidly in alkali also, in a reaction which is independent of pH above pH 10. This reaction is buffer catalysed, and the points on the pH–rate profile (Figure 1) below pH 12 represent (linear) extrapolations to zero buffer concentration. The data for pH >3 were fitted (least squares programme) to the equation $k_{obs} = k_o - a_H k_{obs}/K_a$, which assumes that reaction involves only the free base form of (7), and the pH–rate profile shown is calculated from the results obtained (Table 1). Buffer catalysis constants (Table 2) were also calculated (least squares) on the assumption that the free base of amine (7) is the reactive species, and were consistent with a simple general acid catalysed reaction. The catalytic constants depend only weakly on the $pK_a$ of the general acid; the Brønsted coefficient calculated from the data of Table 2 is 0.15 ± 0.01.

Solvent deuterium isotope effects were measured for the spontaneous reaction in the pH-independent region (0.15M-NaOD) and for the reaction catalysed by phosphate buffer. The pH of the phosphate buffer varied with concentration, from 7.43 to 7.58 over the range 0.04—0.32M, and the

TABLE 2

Buffer catalysis of the cyclisation of (7)[a]

| Buffer (% free base) | pH | Runs | $k_2$/l mol$^{-1}$ s$^{-1}$ |
|---|---|---|---|
| Formate (25) | 3.35 | 9 | 8.41 ± 0.13 × 10$^{-6}$ |
| Acetate (20) | 4.38 | 8 | 3.90 ± 0.29 × 10$^{-5}$ |
| Acetate (55) | 5.20 | 8 | 1.72 ± 0.12 × 10$^{-4}$ |
| Acetate (80) | 5.66 | 6 | 2.21 ± 0.41 × 10$^{-4}$ |
| Phosphate (51.5) | 6.81 | 12 | 3.77 ± 0.28 × 10$^{-3}$ |
| Phosphate (67) | 7.43 | 6 | 1.57 ± 0.07 × 10$^{-2}$ |
| Phosphate (67, in $D_2O$) | 7.50 [b] | 6 | 5.74 ± 0.38 × 10$^{-3}$ |
| Tris (50) | 8.41 | 9 | 8.09 ± 0.09 × 10$^{-2}$ |
| Carbonate (50) | 10.23 | 6 | *c* |
| Brønsted coefficient | −0.15 ± 0.01 | | |

[a] Conditions as for Table 1. Buffer concentrations 0.1—0.5M. [b] pD, uncorrected. $k_H/k_D$ 1.95 (2.73 uncorrected, see text). [c] Second-order plot had negative gradient.

second-order plots for $H_2O$ and $D_2O$ required quite large corrections for the resulting changes in the fraction of substrate (7) in the reactive free base form. Each point was corrected to the pH measured for 0.04M-buffer, using the linear dependence of log $k_o$ on pH in this region. No absolute correction for the fraction of substrate present in the free base form was possible in $D_2O$, because the $pK_a$ is not known in the deuteriated solvent. A measure of the different proportions of substrate free base at the same concentrations of the same buffer in $H_2O$ and $D_2O$ (and thus

of the different isotopic effects on the p$K_a$ values of substrate and buffer) is the apparent solvent deuterium isotope effect on the spontaneous reaction, $k_0^H/k_0^D$, obtained by extrapolating the buffer catalysis plots to zero buffer concentration in $H_2O$ and $D_2O$. The value obtained in this way is 2.46. The correct value, measured without complications in the pH-independent region, is 1.70. Evidently there is 2.46/1.70 times more substrate free base in $H_2O$ than in $D_2O$ in a given phosphate buffer solution. We use this factor to correct the apparent deuterium isotope effect on the phosphate catalysed reaction, from 2.73 to 1.89.

Thermodynamic parameters were measured with some care, in 0.01M-NaOH. At least six runs at each of eight different temperatures in the range 16.5—39° gave the results shown in Table 1.

## DISCUSSION

The evidence available in the literature,[7-10] and the results summarised in Figure 1, show that we are dealing with two quite distinct reactions. The cyclisation of amine (8) is slow in acid, but not detectable above pH 4, whereas the transannular reaction of amine (7), which goes at about the same rate in acid (half-life *ca.* 100 h at 25° in 1M-HCl), is very fast at high pH, with a half-life of 3.3 s in the pH-independent region above pH 10. We discuss first this high pH reaction, which is still rapid at pH 7 ($t_{\frac{1}{2}} < 1$ min at 37°), and is thus precisely the sort of reaction we set out to find.

The pH–rate profile for the cyclisation of (7) depends on an apparent p$K_a$ of 8.77, in the region expected for a tertiary *N*-benzylamine. The observed reaction at pH >3 can be accounted for completely in terms of the cyclisation of the free base form. The remarkable rate of the reaction is a result of a low enthalpy of activation (13 kcal mol$^{-1}$), partly offset by a significantly negative entropy of activation ($\Delta S^{\ddagger}$ −18 cal K$^{-1}$ mol$^{-1}$). This low value of the entropy term falls in the region generally considered characteristic of bimolecular reactions [13] in aqueous solvents, and is consistent, for a pH-independent reaction, with the involvement of a molecule of water in the transition state. So too is the solvent deuterium isotope effect, $k_H/k_D$ 1.70.

The reaction is catalysed by the buffers used to maintain pH. Measurements at three different acetate–acetic acid ratios are consistent with general acid catalysis by the buffer acid of the cyclisation of the free base form of the substrate. (The kinetically equivalent general base catalysis of the reaction of the conjugate acid of the substrate can be ruled out, since *partial* removal of the proton can provide no kinetic advantage over the reaction of the fully deprotonated free base, which is present in substantial amounts above pH 7—8.) The data (Table 2) for a series of five general acids with p$K_a$ values in the range 3.77—8.2 are correlated by the Brønsted equation, with the low exponent $\alpha$ 0.15 ± 0.01. The points for catalysis by both $H_3O^+$ and $H_2O$ show negative deviations from the least squares line, suggesting that the Brønsted plot is curved when general acids of a sufficiently wide range of p$K_a$ are used [14] (Figure 2). Catalysis by dihydrogenphosphate is characterised by a solvent deuterium isotope effect, $k_H/k_D$ 1.89, similar to

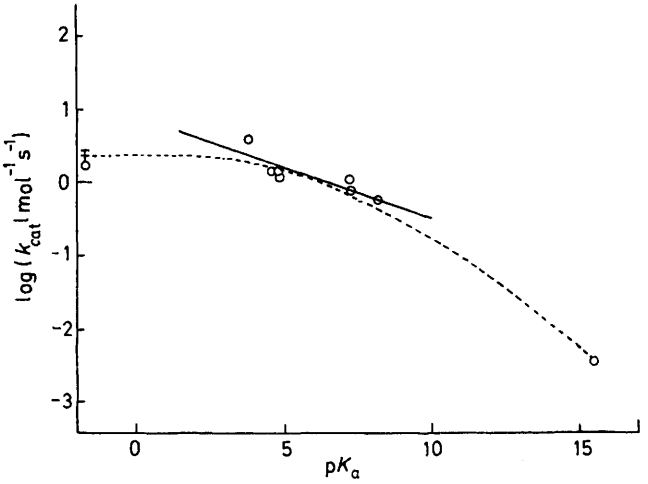
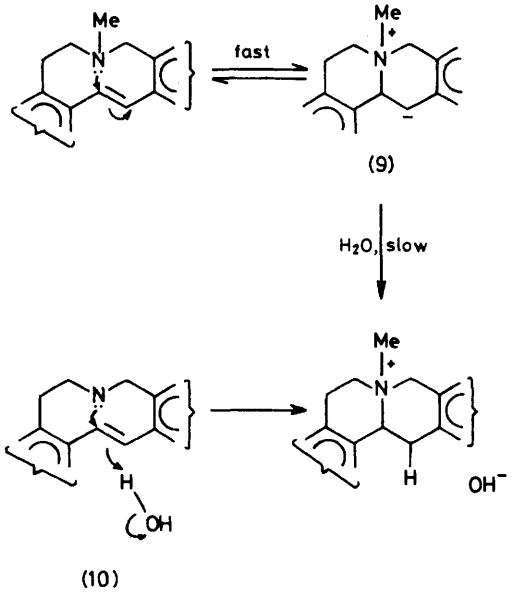



FIGURE 2 Brønsted plot for general acid catalysis of the cyclisation of amine (7) in 20% dioxan–water at 25°. Data are from Table 2. The point for $H_3O^+$ is calculated from the rate constant measured near pH 2 (see Figure 1), and that for $H_2O$ by dividing the rate constant in the pH-independent region above pH 10 by 55

that found for the water reaction, consistent with similar mechanistic roles for water and other general acids.

For this relatively simple reaction, involving the addition of a tertiary amine and a proton to a C=C




SCHEME 2

double bond, this is enough evidence to allow conclusions about mechanism. Initial protonation of the stilbene double bond by water does not seem likely: the base (7) shows a stilbene chromophore in the u.v. region,[10] and

[13] L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 7; W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969, p. 609.

[14] R. P. Bell, 'The Proton in Chemistry,' Chapman and Hall, London, 1973, 2nd edn., p. 195.

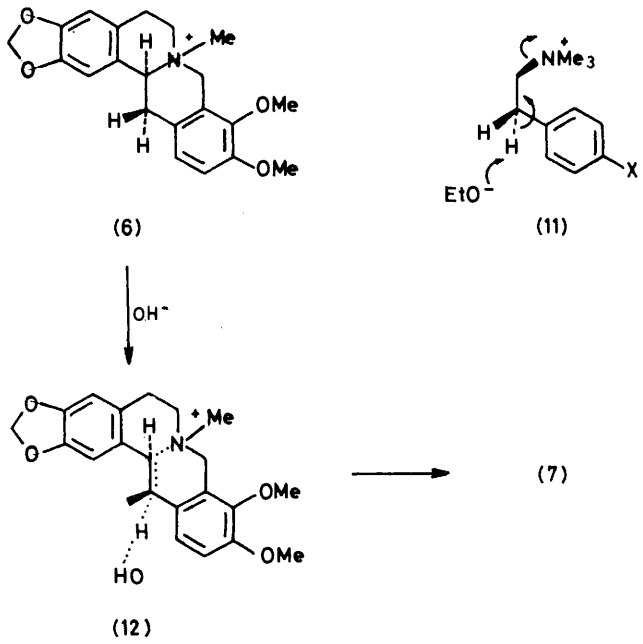
protonation by $H_3O^+$ is on nitrogen. So the problem of mechanism resolves to a choice between rate-determining protonation of a carbanion (9), formed in a rapid pre-equilibrium, and a concerted process (10) which avoids this intermediate (Scheme 2).

The concerted mechanism seems the more likely, for several reasons. Most convincing is the high stereospecificity of the reaction: the observed antiperiplanar addition is readily explained if addition is concerted, whereas there is no obvious reason why the protonation of the carbanion (9) should be stereospecific. Furthermore, the protonation of such a reactive carbanion, stabilised only by the adjacent electron-rich ring, would be very fast, yet the two-step mechanism requires it to be slower than the collapse of the carbanion (9), with the elimination of the tertiary amine, to highly strained starting material. Finally, this pathway is the microscopic reverse of the *E*1cb mechanism, which is normally observed only where the carbanion is rather effectively delocalised.[15]

If the reaction is concerted [(10)] the extent of proton transfer in the transition state is presumably very high or very low,[16,17] to account for the low solvent deuterium isotope effect. The magnitude of the Brønsted exponent, $\alpha$ 0.15, for general acid catalysis is consistent with a very low degree of proton transfer from water to carbon. Thus the evidence favours the concerted process (10), with an early transition state. This is consistent with all the evidence available for our reaction. It is also in line with current thinking on the reverse reaction.

Several authors are agreed that the ethoxide-catalysed elimination of trimethylamine from 2-arylethyltrimethylammonium ions (11) is a normal *E*2 process with a late (carbanion-like) transition state.[18-20] The primary deuterium isotope effect is low [$k_H/k_D$ 2.64 at 40° for (11; X = OMe)] [19] compared with values observed for similar compounds with better leaving groups [18] or with electron-withdrawing substituents X,[19] and the Hammett reaction constant is large and positive. On the basis of these results we can make specific predictions about the transition state (12) for the formation of (7) from *N*-methyltetrahydroberberine (6) and hydroxide.

The reaction is expected to be an *E*2 process like the similar reactions of other (substituted phenyl)trialkylammonium ions (11), but the strain associated with the ten-membered ring of (7) will presumably make the amine nitrogen a significantly poorer leaving group than trimethylamine. This should mean a later, more product-like transition state.[21,22] Extrapolating from the results of Smith and Bourns [19] we can therefore predict a primary deuterium isotope effect, $k_H/k_D$, in the region of 2 * [and a nitrogen isotope effect, similarly larger than that observed for the reaction of (11; X = OMe)]. (12) is of course the same transition state, approached from the opposite direction, as that for the reverse




Hofmann elimination (10). It is encouraging that the two independent descriptions are in close agreement for all the points they have in common. Combining the evidence from the two approaches we arrive at a detailed picture of the transition state (10), for the transannular addition of amine nitrogen to the stilbene double bond, with C–N bond formation not far advanced, a significant development of negative charge at C-13, little bond formation from C-13 to the proton of the general acid, and with the bond between this proton and the conjugate base of the general acid largely intact.

*Structure and Reactivity.*—This mechanism is not unexpected. Indeed, Haworth, McKenna, and their co-workers made just this suggestion to account for their slow reverse Hofmann eliminations [*e.g.* (4) ⟶ (5)].[7e,8] If a nucleophile does add to an unactivated carbon–carbon double bond under neutral or basic conditions in a protic solvent it is almost inevitable that the developing carbanion will be neutralised by the solvent at an early stage. Yet clear cut examples of concerted general acid catalysis of nucleophilic addition to double bonds have proved very elusive. Nucleophilic addition to $sp^2$ hydridised carbon normally occurs only when the $\pi$-system is polarised by an electronegative element, so that

* $k_H/k_D$ for elimination reactions of (11) is reduced by electron donation, and for poorer leaving groups.[19] So the isotope effect for reaction through transition state (12) is expected to be less than 2.64 [observed for (11; X = OMe)] because of the introduction of the second methoxy-group, and in so far as strain in (7) makes the tertiary nitrogen atom of (6) a poorer leaving group than trimethylamine.

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[16] F. H. Westheimer, *Chem. Rev.*, 1961, **61**, 265.

[17] W. H. Saunders, jun., and A. F. Cockerill, 'Mechanisms of Elimination Reactions,' Wiley, New York, 1973, pp. 71*ff*.

[18] W. H. Saunders and D. H. Edison, *J. Amer. Chem. Soc.*, 1960, **82**, 138; see also ref. 17, p. 80.

[19] P. J. Smith and A. N. Bourns, *Canad. J. Chem.*, 1974, **52**, 749.

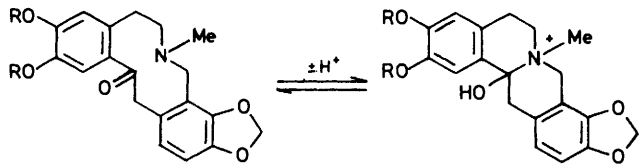
[20] W. H. Saunders, D. G. Bushman, and A. F. Cockerill, *J. Amer. Chem. Soc.*, 1968, **90**, 1775.

[21] L. J. Steffa and E. R. Thornton, *J. Amer. Chem. Soc.*, 1967, **89**, 6149.

[22] E. R. Thornton, *J. Amer. Chem. Soc.*, 1967, **89**, 2915.

initial proton transfers are fast, diffusion-controlled processes.*

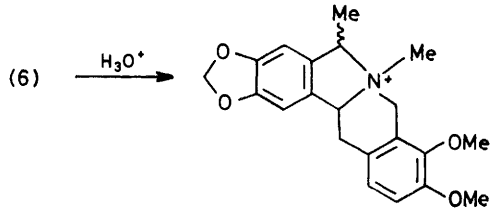
The special factor responsible for the rapid cyclisation of amine (7), and for the concerted mechanism, must be ground state strain, which is relieved in the transition state for cyclisation. It is well known that transannular interactions are high in ten-membered rings. The conjugate acids of the alkaloids protopine (13; $R_2 = CH_2$) and cryptopine (13; R = Me), for example, show no carbonyl absorption in the i.r. region,[25] because they are cyclised to carbinolamines (14).[26] The formation of the transannular bond relieves the ground state strain present in the conjugate bases (13), as revealed by *X*-ray crystal structure analyses.[27] The short transannular N–C(O) distances (<2.6 Å, nearly 20% less than the sum of the van der Waals radii), and associated deformations from planarity of the carbonyl group, have been taken as evidence that these structures represent amine to ketone addition reactions, frozen part-way along the reaction co-ordinate by the constraints of molecular and crystal structure.[28]




(13) (14)

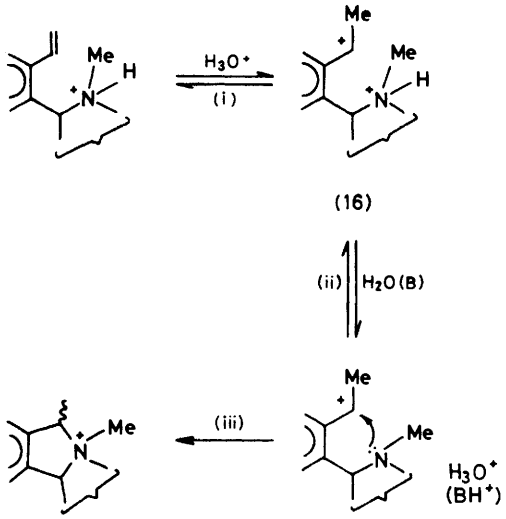
There seems no reason to doubt that similar factors control the reactivity of amine (7). The base could not be crystallised in a form suitable for *X*-ray structure determination, but space-filling models show a medium ring with little flexibility and large transannular interactions. The nitrogen lone pair is held very close to the π-system of the stilbene double bond, above C-14. [Dreiding models indicate a transannular N–C-14 distance comparable with that in the more flexible protopine structure (13).]

Our main conclusion is therefore that no more than the appropriate juxtapositioning of a double bond and an amino-group is sufficient for very ready C–N bond formation in protic media, even when the double bond carries no activating substituents. ' Appropriate juxtapositioning ' involves, in particular, significant ground state strain which is relieved on bond formation. In other words the nitrogen has to be to some extent ' forced ' onto the receptor carbon. This readily explains the high sensitivity to structure of the reaction, which is known to proceed readily only in the case of (7), and very slowly for two other specially favourable intramolecular reactions.[7e,8] We are not able to make an accurate estimate of the effective molarity of the intramolecular nucleophile in this reaction, because the corresponding intermolecular reaction is not observed. The best available model is the addition of ammonia to the fumarate dianion,[4] though the olefin must be considered significantly activated, as discussed above. From Bada and Miller's data we calculate a rate constant of about $10^{-9}$ dm$^3$ mol$^{-1}$ at 25°, suggesting that the effective molarity of the tertiary nitrogen of amine (7) is greater than 10$^8$M.




(15)

*The Acid-catalysed Reaction.*—The cyclisation of amine (7) is faster in 1M-HCl than at pH 2 (Figure 1) which suggests that the cyclisation of the protonated form of (7) is catalysed by acid. The rate at pH 2 is higher than can be accounted for by adding the contributions from this acid catalysed reaction and the spontaneous reaction of the free base form of (7), and is consistent with an $H_3O^+$ catalysed reaction of the free base [which will be pH-independent in the region where (7) is present as the conjugate acid]. We have investigated the $H_3O^+$ catalysed reaction of the conjugate acid, using amine (8), which reacts at a similar rate in 1M-HCl, but does not cyclise at a measurable rate above pH 4.




SCHEME 3

* The hydration of strained olefins is sometimes general acid catalysed,[23] but the rate-determining step appears to be just the initial proton transfer. Increasing ground state strain simply results in an earlier transition state.[24]

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[27] S. R. Hall and H. Ahmed, *Acta Cryst.*, 1968, **24B**, 337, 346.

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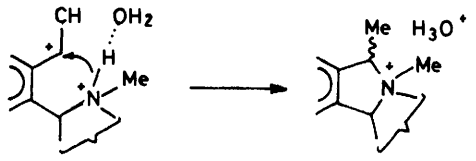
This is found to be a specific acid catalysed reaction. log $k_{obs}$ is a linear function of pH, with a slope of −1, and the rate does not depend on the concentration of chloroacetate buffer at pH 2.4. The product of the reaction is not *N*-methyltetrahydroberberine (6), but almost certainly the five-membered ring product (15) of addition of nitrogen to the other end of the styrene double bond, as a mixture of comparable quantities of epimers.

This reaction involves three distinct operations: protonation of the styrene double bond, removal of the




(16)

SCHEME 4

proton from nitrogen, and addition of nitrogen to the double bond. If any one of these steps were rate determining, general acid catalysis would be expected. This is readily apparent for the proton transfer steps [steps (i) and (ii) of Scheme 3]. And the rate law requires that the hydroxonium ion generated in step (ii) does not diffuse away before the addition of nitrogen to the neighbouring carbonium ion, if step (iii) is rate determining for the $H_3O^+$ catalysed reaction.

The most likely mechanism remaining involves rate determining electrophilic attack by the carbonium ion (16) on the $\overset{+}{N}H$ bond, which will normally be hydrogen-bonded to solvent water (Scheme 4). Note that this mechanism differs significantly from normal general base catalysed addition of a nucleophile to an electrophilic centre,[14] since an ammonium ion is not initially a nucleophile at all. The solvating molecule will normally be water rather than a general base, since a carboxylate ion, for example, will be separately solvated in water. General species catalysis is not therefore to be expected.

This mechanism must remain tentative, though it is difficult to think of a reasonable alternative consistent with the evidence. It is proposed to account not only for the cyclisation of amine (8), but for the great majority of reverse Hofmann eliminations [7,8] which go in acid but not under neutral or basic conditions.

*Conclusions.*—Two distinct mechanisms account for the reverse Hofmann elimination. The reaction as normally carried out under acidic conditions involves the protonation of the double bond, to generate the more stable carbonium ion, followed by rate-determining attack on the neighbouring ammonium centre. The efficiency of this reaction is evidently sensitive to entropic factors,[29] but is not significantly enhanced by ground state strain [(7) and (8) are cyclised at similar rates in acid].

The second mechanism is only observed in cases where substantial ground state strain is relieved on cyclisation, and involves nucleophilic addition of amine nitrogen to the olefinic double bond, concerted with protonation by a general acid. The regiospecificity is controlled by the geometry of the system.

It is this mechanism which is of interest in connection with enzyme catalysed addition reactions. This work shows that the appropriate juxtapositioning of nucleophile, double bond, and general acid, which could be provided by the substrate binding step, can lead to ready, stereospecific addition to an unactivated double bond.

[7/1577 *Received*, 5*th September*, 1977]

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